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What genome-wide association studies reveal about the association between intelligence and mental health

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Intelligence, as measured by standardised tests of cognitive function, such as IQ-type tests, is predictive of psychiatric diagnosis and psychological wellbeing. Using genome-wide association study (GWAS) data, a measure of the shared genetic effect across traits, can be quantified; because this can be done across samples, the confounding effects of psychiatric diagnosis do not influence the magnitude of these relationships. It is now known that there are genetic effects that act across intelligence and psychiatric diagnoses, which provide a partial explanation for the phenotypic link between intelligence and mental health. Potential causal effects between intelligence and mental health have been identified, and the regions of the genome responsible for some of these cross trait associations have begun to be characterised.

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Intelligence and mental health

Intelligence, sometimes called general cognitive ability/function, the *g* factor, or simply *g*, describes the finding that scores on cognitive tests that each seem to tax disparate aspects of mental ability, positively correlate [1]. This overlap accounts for around 40% of the variance found when administering a broad array of cognitive tests to a group with a range of ability [2,3]. This finding has been known for over a century, and has been replicated in hundreds of data sets [1–3].

Individual differences in intelligence are predictive of mental illness, where a higher level of intelligence in childhood is predictive of a lower level of self-reported

psychological distress decades later [4]. This link between intelligence and mental illness also extends to severe psychiatric conditions where individuals who have a level of intelligence one standard deviation below the mean have, on average, a 60% greater chance of being hospitalized for schizophrenia, a 50% increase of being diagnosed with a mood disorder, and a 75% greater risk for having an alcohol-related disorder, over a two-decade follow up period [5]. A higher risk for several psychiatric illnesses has also been associated with a lower level of intelligence, including major depressive disorder (MDD) [6,7], autistic spectrum disorder (ASD), attention/deficit hyperactivity disorder (ADHD) [8], as well as bipolar disorder [9,10], although a higher level of intelligence, particularly as measured by tests of crystallized ability, may also be a risk factor for bipolar disorder [11].

Genetic architecture of intelligence and mental health

Intelligence, like many other quantitative traits [12,13], is heritable with twin and family derived estimates of heritability being around 50–80% [14], with genetic factors explaining an increasing proportion of variance as the age of the sample increases [15]. Molecular genetic data can also be used to derive the proportion of phenotypic variation explained by all genome-wide single nucleotide polymorphisms (SNPs), using genomic-relatedness-based restricted maximum-likelihood single component (GREML-SC) [16], implemented in GCTA [17]. Heritability estimates derived using GREML-SC describe the proportion of phenotypic variance that is explained by genetic variants in linkage-disequilibrium (LD), that is to say correlated, with genotyped SNPs. As SNP arrays typically measure common genetic variation, and two events can only be highly correlated if they occur with a similar frequency, GREML-SC estimates of heritability represent a subset of the total heritability in phenotypes where the genetic architecture includes contributions from low frequency variants, and other types of genetic variation that are poorly correlated with common SNPs. Heritability estimates derived using GREML-SC applied to intelligence show that around 22.7% (SE = 2.1%) of phenotypic variance is explained by additive genetic effects that are linked to common SNPs [18**]. Psychiatric disorders have also been shown to be heritable using GREML-SC, where additive common genetic effects explain 23% (SE = 0.8%) of schizophrenia [19], 21% (SE = 2.1%) of MDD [19], 28% (SE = 2.3%) of ADHD [19], 25% (SE = 1.2%) of bipolar disorder [19], 17% (SE = 2.5%) of ASD [19], and 10.8% (SE = 2.0%) of

neuroticism [18**], an individual's propensity to experience psychological distress.

A method to capture genetic effects from across the frequency spectrum of causal variants, called GREML-KIN [20], has been applied to intelligence, neuroticism, and MDD. For intelligence 54.0% of phenotypic variation can be explained using genome-wide association (GWAS) data [18**]. For neuroticism, 30% of phenotypic variation is captured, with 47.0% of MDD [21] being explained by additive genetic effects when common and rare genetic effects are summed.

GWAS for intelligence have recently attained the statistical power required to reliably identify the loci that contribute to these heritability estimates with more than 200 being identified so far [22**,23**,24] (15 novel loci identified in Snickers *et al.*, 130 novel loci identified in Hill *et al.*, and 58 novel loci identified in Davies *et al.*). However, the total proportion of variance these loci explain is far lower than the substantial heritability estimates. This 'missing heritability' [25] is also seen when examining psychiatric variables and is indicative of a highly polygenic architecture, where the cumulative effect of all genetic effects may be substantial, but the contribution made by any individual variant is negligible. This substantial heritability, combined with the relative sparsity of loci identified at current sample sizes, is compelling evidence that by increasing sample size, and with it the ability to reliably estimate small effects, will result in an increase in the number of loci identified for both intelligence and psychiatric variables. Figure 1a shows the Manhattan plot from one of the first well powered GWAS on intelligence [22**].

Genetic links between intelligence and mental health

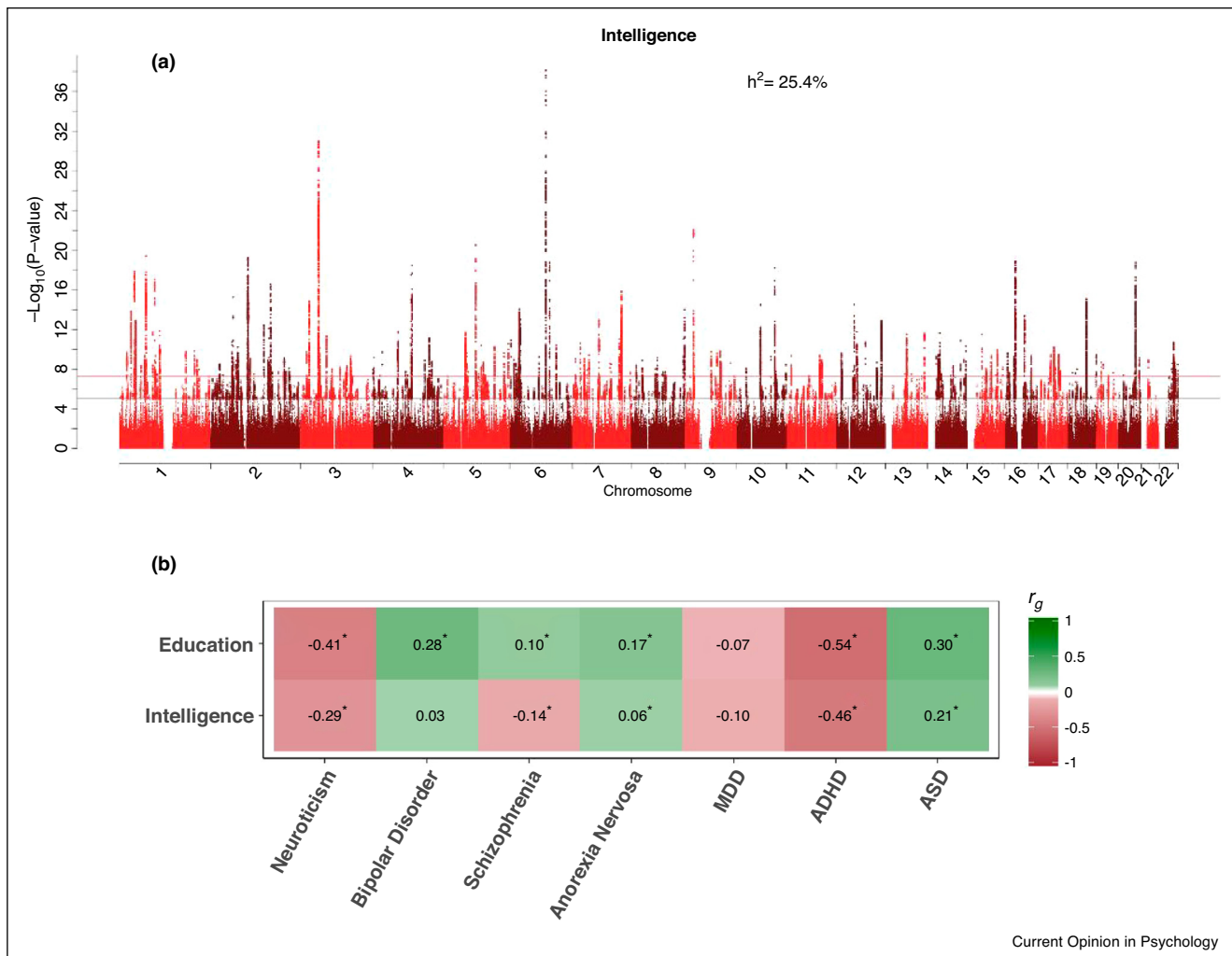
The polygenic signal that drives heritability estimates can also be used to derive genetic correlations to describe the average genetic effect that is attributable to causal variants in LD with common SNPs, and shared across two traits. Using a technique called linkage disequilibrium score (LDSC) regression [26,27**] genetic correlations between two GWAS data sets can be derived. Whilst LDSC regression is less precise than GREML, as indicated by the higher SE even when sample sizes are similar, as well as in instances where there is genetic heterogeneity between the reference panel used to derive LD scores and the sample used to derive the genetic correlations [28], LDSC regression has the advantage that the GWAS data can come from separate samples where individual level data is unavailable. Although an overlap in controls is not uncommon, by performing genetic correlations across data sets neither the symptoms of psychiatric diagnosis, hospitalisation, or drug regimens, can confound the measure of the genetic relationship between intelligence and psychiatric illness.

When applied to GWAS on intelligence and psychiatric disorders, both positive and negative genetic correlations are found. Anorexia nervosa, for example, shows a small but statistically significant positive genetic correlation with intelligence ($r_g = 0.06$, $SE = 0.03$, $P = 0.02$), as does ASD ($r_g = 0.21$, $SE = 0.04$, $P = 2.46 \times 10^{-8}$) [22**]. Negative genetic correlations however, are found between intelligence and schizophrenia ($r_g = -0.14$, $SE = 0.03$, $P = 1.49 \times 10^{-9}$), ADHD ($r_g = -0.46$, $SE = 0.03$, $P = 2.41 \times 10^{-54}$), neuroticism ($r_g = -0.29$, $SE = 0.07$, $P = 7.01 \times 10^{-6}$) [22**], and more recently with MDD ($r_g = -0.30$, $SE = 0.04$, $P = 1.28 \times 10^{-13}$) [23**]. Together this indicates that the genetic variants associated with high levels of intelligence have both protective and facilitative effects on the genetic liability of mental illness, with the genetic variants associated with a decrease in neuroticism, MDD, and schizophrenia being, on average, those linked to higher levels of intelligence, and genetic variants that confer greater risk of ASD, and of anorexia nervosa also being linked to higher levels of intelligence. Bipolar disorder, however, shows a genetic correlation of around zero with intelligence [22**,29**].

Educational attainment (as measured by the number of years in education or by whether an individual attained a University or college level degree) shows a strong genetic correlation with intelligence ($r_g = 0.70$, $SE = 0.02$, $P = 1.28 \times 10^{-285}$) [22**] and has been used as a proxy phenotype for intelligence [30]. However, in contrast with intelligence the genetic architecture of education shows a positive genetic correlation with schizophrenia ($r_g = 0.10$, $SE = 0.02$, $P = 5.40 \times 10^{-6}$) [22**] and with bipolar disorder ($r_g = 0.28$, $SE = 0.04$, $P = 4.84 \times 10^{-14}$) [22**]. This indicates that, on average, the genetic variants associated with an increase in educational attainment are also linked to an increase in the risk of both schizophrenia, and bipolar disorder, despite that the genetic variants associated with an increase in intelligence are also linked to a reduction in the genetic risk for schizophrenia and are not linked to bipolar disorder. This difference between how the genetic aetiology of intelligence and education overlap with schizophrenia and bipolar disorder, can serve as a diagnostic tool to gauge whether a phenotype constructed to measure intelligence, is in fact a better measure of educational attainment [31]. Figure 1b shows the genetic correlations between intelligence, as well as education, with six psychiatric disorders and neuroticism.

Whereas the large genetic correlation between intelligence in childhood, and intelligence in older age ($r_g = 0.71$, $SE = 0.10$, $P = 2.26 \times 10^{-12}$) suggests that many of the same variants are involved in intelligence across the lifespan, the overlap between intelligence and psychiatric variables may be influenced by the age at which intelligence was assessed [29**]. This may be due to the genetic contributions to intelligence, as measured

Figure 1



Panel A shows a Manhattan plot from one of the first well powered GWAS on intelligence [22**]. The X axis shows the autosomal chromosomes labelled 1 to 22, and the Y axis shows the $-\log_{10}$ of the P value. Each of the red dots indicates a SNP, a unit of genetic variation, those that cross the red line withstood correction for multiple comparison ($P < 5 \times 10^{-8}$). The heritability (h^2) of intelligence, as derived using all SNPs in Panel A, was 25.4%. Panel B shows the genetic correlations between intelligence and measures of mental illness and neuroticism. Red indicates a negative genetic correlation and describes a situation where the genetic contributions for higher intelligence are linked to a lower genetic risk of disorder. Green indicates a positive genetic correlation, and describes a relationship where the genetic variants associated with an increase of intelligence, are also linked to a risk of disorder. Also plotted are the genetic correlations between education and the mental health variables, of note, is that the genetic variants linked to educational success are also linked to a higher genetic risk of schizophrenia, whereas the opposite is true for intelligence. Asterisks indicate genetic correlations that withstood correction for multiple tests in the original publication [22**].

in childhood, being a product of genetic effects involved in the development of intelligence, whereas intelligence in older age will also be a product of the genetic effects involved in the maintenance of intelligence across the life course [29**].

Shared loci between intelligence and mental health

Genetic correlations tell us about the average genetic effect that is shared across traits. As such, they do not identify the variants involved in cross-trait associations,

nor do they imply that when such a variant is identified it will have a shared effect on the two traits consistent with the direction of effect of the genetic correlation. One way to identify loci with a shared effect is to examine SNPs that attain genome-wide significance in intelligence, and in psychiatric disorders. However, this method is dependent on the number of genome-wide significant SNPs. In contrast to examining if a SNP is genome-wide significant in two traits, conjunctive false discovery rate [32] (cFDR) can be used to determine if a SNP shows association with two traits simultaneously. cFDR has been used

to examine the genetic link between schizophrenia and intelligence by identifying loci that harbour joint effects. A total of 21 loci were identified as acting across schizophrenia and three measures of cognitive ability (two measures of intelligence, and one measure of reaction time). The genes that were implicated using the cFDR approach were expressed across the developing and adult brain consistent with the strong genetic correlations between childhood intelligence and older age intelligence. Again consistent with the genetic correlations between intelligence and schizophrenia, 18 of the 21 loci identified contained risk alleles that were facilitative of intelligence and protective against schizophrenia. The remaining three loci harboured variants that were associated with a higher level of intelligence and a greater risk of schizophrenia, consistent with some reports finding that a number of those diagnosed with schizophrenia have retained their level of intelligence [33].

Interpretation of a shared genetic effect

GWAS exploits the correlation between SNPs (whether genotyped or imputed) and unknown causal genetic variants. By doing so, regions of the genome, defined by the correlation between SNPs, are identified as being linked to potentially causal variants. The presence of genetic correlations, loci associated across traits, and even the same SNP being implicated in multiple traits, can therefore arise in a number of different conditions.

Firstly, biological pleiotropy may be in effect and can be the result of a single SNP, that is genome-wide significant in two traits, tagging a single variant that is causal in both of the studied phenotypes [34^{*}]. Alternatively, biological pleiotropy can describe a situation where a single SNP, again genome-wide significant in two GWAS, tags two causal variants (each causal for a different phenotype) that are both in the same gene. Biological pleiotropy can also describe a situation where two SNPs, both within the same gene, each tag independent causal variants that are also located within the same gene.

Secondly, mediated pleiotropy can occur where one phenotype is a causal element in a second phenotype. In such instances genetic variants identified for the causal trait will also be associated with the second. For example, mediated pleiotropy is likely to explain the genetic link between intelligence with education and other measures of socio-economic status [22^{**},35].

Finally, spurious pleiotropy can occur where there is misclassification of the phenotype, this can occur if the low mood observed by those with bipolar disorder is misclassified as MDD or in cases where those with bipolar disorder are misdiagnosed as having schizophrenia. In these instances, a genetic correlation will exist between these traits that is due to contamination of samples, rather than genetic effects that act across traits. Spurious

pleiotropy can also occur in cases where a single variant is found to be associated with two traits, but this variant is tagging two, independent causal variants, each of which is found in a different gene. This can occur in regions of the genome where there is strong linkage disequilibrium. As genetic correlations are based on all SNPs within a data set, different forms of pleiotropy may be in effect.

Whereas genetic correlations and shared risk loci are informative as to the average genetic effect across traits, as well as the regions of the genome where such effects are localised, they are not informative as to causality. Mendelian Randomisation (MR) can be used to mimic a randomised control trial using observational (GWAS) data under a number of assumptions [36,37]. MR typically uses SNPs that have attained genome-wide significance for a trait, such as intelligence, as proxy variables for the trait. Independent groups can then be made by grouping participants according to genotype. Groups that are created in this way will also be grouped according to the phenotype, in this case intelligence, that is linked to the genotype. As genetic variants are assigned randomly to a child at conception, MR can be seen as a randomised control trial where intelligence, is randomly assigned to a participant at conception.

Using MR, causal links have been suggested for the link between intelligence and education [38^{**}], and this relationship appears to be bidirectional with education being a causal factor in intelligence differences. A bi-directional causal relationship has also been seen for schizophrenia where higher levels of intelligence appear to be causally linked to a risk of schizophrenia [38^{**}]. Lower levels of intelligence also appear to exert a causal risk on ADHD [38^{**}], and consistent with the direction of the genetic correlation, and a higher level of intelligence is a causal risk for ASD [38^{**}].

To conclude, intelligence and psychiatric illnesses are highly polygenic traits where common and rare genetic effects appear to be explain a substantial proportion of individual differences. It is the common genetic effects that are known to act on across intelligence and psychiatric disorders and this genetic link between intelligence and psychiatric condition is not confounded by the presence of psychiatric disease, hospitalisation, or treatment regime. The direction of effect is that high intelligence is protective against schizophrenia, MDD, ADHD, and neuroticism, but is a risk factor for ASD, and anorexia nervosa. Loci of shared effect have been identified for intelligence and schizophrenia implicating brain expressed genes that are expressed in developing and adult brain.

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Conflict of interest statement

Nothing declared.

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- of special interest
- of outstanding interest

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